REMARKS

Claims 12-14 and 18 are pending in this application. Claims 12, 13, and 18 have been amended. Claims 22-29 have been added as supported throughout the specification and at page 40, lines 12-24 (claims 22-26); page 3, line 3(claim 27); and at page 41 line 32 through page 42, line 2 (claim 28-29). No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks and amendments.

I. Rejection of Claims 12-14 and 18 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 12-14 and 18 under 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these claims. Specifically, the Examiner has raised issues with regard to three different subject area, namely the delivery system and mode of administration, nature of the carboxylesterases, and the selected prodrug.

The Examiner has acknowledged that the specification is enabling for a method of sensitizing tumor cells to

chemotherapeutic prodrug APC or CPT-11 *in vitro,* comprising transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter directs specific expression of said carboxylesterase in said tumor cells, wherein expression of said carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic drug. It is further acknowledged that a method of inhibiting tumor cell growth *in vitro* comprising sensitizing tumor cells by transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter which directs specific expression of said carboxylesterase in said tumor cells and contacting said tumor cells with chemotherapeutic prodrug APC or CPT-11 so that the tumor growth is inhibited is enabled. However, it is suggested that the specification does not reasonably provide enablement for a method for *in vivo* application wherein the polynucleotide encodes any carboxylesterase and the said enzyme and wherein the chemotherapeutic drug is delivered by any route. Applicants respectfully disagree.

The Examiner suggests that the instant specification only supports the claimed invention for *in vitro* but not in an *in vivo*

setting over the full scope. The Examiner acknowledges that the animal model is considered to be sufficient in the case of *In re Brana* for testing chemical compounds because the purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. However, it is suggested that Applicants are claiming a method of sensitizing tumor cells and a method of inhibiting tumor growth both *in vitro* and *in vivo* by administering a nucleic acid encoding a carboxylesterase which can activate chemotherapeutic prodrug APC or CPT-11. The Examiner acknowledges that the claimed method may have potential utility in humans but, suggests that the Examiner does not believe that the method can be practiced to its fullest scope without undue experimentation. The Examiner suggests that the art of gene therapy as a whole is unpredictable. The Examiner further states that the only concern is enablement not utility.

The Examiner has acknowledged that the Declaration filed on November 18, 2002 (Declaration 1) demonstrates that intravenous or intratumoral injection to a mouse model carrying the rabbit carboxylesterase renders the tumor cells more sensitive to the chemotherapeutic agent CPT-11. Declaration 1 is further acknowledged to demonstrate that such effect is achieved by

increasing intracellular level of active metabolites SN-38 due to carboxylesterase activity. It is yet further acknowledged that a method for sensitizing tumor cells to chemotherapeutic prodrug APC or CPT-11 *in vitro* is clearly supported, comprising transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter which directs specific expression of said carboxylesterase in said tumor cells; wherein expression of said carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic drug.

The Examiner suggests however, that all the references cited by the Applicants in Declaration 1 fail to teach the effectiveness of gene therapy beyond intratumoral delivery. This data is suggested to fail to enable a method wherein the nucleic acid encodes any carboxylesterase, and co-administration of any chemotherapeutic prodrug. Applicants respectfully disagree.

A. Delivery System and Mode of Administration

First, there is no reason to limit the mode of administration of the chemotherapeutic prodrug of the present invention to intravenous only, as suggested by the Examiner.

Applicants have clearly taught multiple routes of delivery to tumor sites in addition to intravenous administration, page 28, line 10 teaches systemic administration (not intravenous only)of a prodrug; page 28, lines 23-25 of the specification further teaches that administration modes are well known to those of skill in the art. For example, attached is a package insert for Xeloda, a capecitabine class prodrug, is shown to be capable of oral administration. The page insert is dated April 7, 1998. Xeloda is cleaved in the liver by carboxylesterase to 5-fluorouracil. The Examiner has not provided any reason why the these routes of administration as described in the specification would not work.

Second, to further address the Examiner's enablement rejection concerning the delivery system, Applicants are submitting a second Declaration (Declaration 2) from the co-inventors (attached herewith) which explains why the Examiner's assertions are incorrect, and which further corroborate that the instant application enables one of skill in the art to practice the instant claimed invention. The present invention teaches a method for sensitizing tumor cells to a chemotherapeutic prodrug comprising transfecting selected tumor cells with a composition comprising an isolated polynucleotide encoding a

carboxylesterase. Support for the use of several different delivery systems is taught throughout the application and at pages 7, lines 6-24; page 28 lines 4-7; and page 28 lines 25-28. Also, in Declaration 1, which was filed with an Office action response on November 18, 2002, *in vivo* data was submitted supporting the use of adenovirus as a suitable vector for delivery of carboxylesterase. As disclosed in the specification at page 28, line 6, and as also shown in the attached Declaration 2 at Figure 1 and paragraphs 3-4, human intestinal carboxylesterase (hiCE) can be expressed from two Herpes simplex viral vectors. The Herpes simplex viral vectors would be an efficient system for delivering carboxylesterase *in vivo*. Furthermore, as taught in the specification at page 7, lines 6-24, other gene delivery systems well known in the art such as retroviruses, vaccinia viruses, adeno-associated viruses, chemical mediated gene transfer, receptor-mediated DNA uptake, neural stem cell, and physical transfer by gene guns or electroporation would also be suitable *in vivo* systems for delivering carboxylesterases. Further, the specification at page 15, lines 12-27, teaches the use of vectors suitable for gene delivery, including: chromosomal, episomal, and virus-derived vectors. Page 28, lines 4-7 of the specification teaches

preferred viral vectors to include retroviral, adenoviral, herpesvirus, vaccinia viral, and adeno-associated viral vectors. Therefore one of skill in the art, would not be required to perform undue research or experimentation, in order to practice the present invention.

Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Nature of Carboxylesterases

The Examiner suggests that the genus of carboxylesterase potentially encompass a large number of enzymes. It is further suggested that the specification only discloses a rabbit carboxylesterase that is capable of cleaving the ester linkage of chemotherapeutic agent CPT-11 and its inactive metabolite APC. Applicants respectfully disagree.

Applicants have clearly taught the use of more than one carboxylesterase in the application. *In vivo* experiments using the human intestinal carboxylesterase are found on page 40, lines 20 through page 41, line 2. Other experiments showing the use of human intestinal carboxylesterase are found throughout the specification. Declaration 2 at paragraphs 6-7 and Figure 2 further show additional information which corroborate that other

CEs could be used in the invention, i.e., a bacterial carboxylesterase is capable of activating CPT-11. Further, the bacterial carboxylesterase was identified using the assays outlined in the specification. It is believed that a person of ordinary skill in the art could routinely identify other carboxylesterases that activate a particular prodrug without undue experimentation. However, in an earnest attempt to facilitate prosecution in this case and secure allowance of the pending claims, claims 12, 13 and 18 have been amended to clarify the present invention in that not all carboxylesterases can be used in the present invention, only those which are capable of cleaving a prodrug. Support for this amendment is found throughout the specification and at page 24, lines 15-24 for predicting carboxylesterases capable of cleaving CPT-11 via a computer modeling method; on page 30, line 8 through page 31, line 3, and on page 35 line 22 through page 36, line 18 for an assay system for testing the carboxylesterase cleaving ability. Claims 22 through 29 have been added to further clarify the invention as supported throughout the specification and at page 40, lines 12-24 (claims 22-26); page 3, line 3(claim 27); and at page 41 line 32 through page 42, line 2 (claim 28-29).

As further corroboration, Declaration 2 at paragraph 6,

shows that yet another carboxylesterase, the pnbA gene from *Bacillus subtilis* is capable of cleaving a prodrug and that this carboxylesterase was identified using the methods described in the specification. An assay provides means for identifying other additional carboxylesterases which is clearly within the skill of one in the art, as taught by the specification at page 30, line 8 through page 31, line 3 and page 35, line 22 through page 36, line 18. Therefore, Applicants have provided methods to identify which carboxylesterases will work without undue experimentation and data proving those methods will work.

Applicants respectfully request reconsideration and withdrawal of this rejection.

C. The Selected Prodrug

It is further suggested that the specification fails to disclose any chemotherapeutic prodrugs other than CPT-11 and APC. Applicants respectfully disagree.

As described above, claims 12, 13 and 18 have been amended to clarify that the prodrug of the present invention is limited to those prodrugs which are capable of being cleaved with a carboxylesterase. Applicants have also shown in the attached Declaration 2 at paragraph 9, that undue experimentation is not required to identify prodrugs capable of being cleaved by

carboxylesterase. A computer model is capable of predicting which prodrugs will be cleaved efficiently by a particular carboxylesterase, see page 24, lines 15-24 of the specification. As stated in Declaration 2 at paragraph 9, the computer model was used to accurately predict rabbit carboxylesterase's ability to cleave BP-CPT. The model predicted that rabbit carboxylesterase would activate BP-CPT less efficiently than CPT-11 which was confirmed by growth inhibition studies and kinetic experiments.

Accordingly, Applicants have shown that drugs other than CPT-11 and APC are capable of being cleaved by a carboxylesterase without undue experimentation. Applicants teachings are further confirmed by the attached package insert for Xeloda, a capecitabine class prodrug, which is shown to be cleaved in the liver by carboxylesterase.

Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached is a Declaration (referenced as Declaration 2 with Figures 1 and 2 and attachments).

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **July 9, 2003**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515